American Journal of Medical Genetics 70:118–120 (1997)

Familial Hydronephrosis Unlinked to the HLA Complex

Alena Šantavá,[1]* Anna Utíkalová,[2] Adéla Bártová,[3] Jiří Drábek,[3] Jiří Šantavý,[1] and Jiří Scheinar[2]
[1]*Department of Medical Genetics and Fetal Medicine, Palacky University, Olomouc, Czech Republic*
[2]*Department of Urology, Palacky University, Olomouc, Czech Republic*
[3]*Department of Immunology, Palacky University, Olomouc, Czech Republic*

Clinical findings, management, and possible linkage of congenital hydronephrosis caused by ureteropelvic junction stenosis to the HLA complex were studied in four families. These families provide evidence of possible autosomal dominant inheritance. HLA class I antigen studies in all four and class II (HLA-DR) in three families were performed. These studies failed to show close linkage to the chromosome 6 markers in two families but there was consistent inheritance in the other two. Although formal linkage calculations are not presented, it is apparent that in some families HLA haplotyping is not useful in predicting prevence of renal obstruction. Am. J. Med. Genet. 70:118–120, 1997.

KEY WORDS: congenital hydronephrosis; automosomal dominant inheritance; HLA system

INTRODUCTION

Congenital hereditary hydronephrosis (HN), caused by obstruction of the ureteropelvic junction region, usually occurs sporadically. However, familial occurrence both in subsequent generations or among siblings has been documented repeatedly. Possible genetic mechanisms involve multifactorial or autosomal dominant inheritance with reduced penetrance. Possible heterogeneity of the disorder may be another factor. HLA studies in some families with HN (performed because of planned renal transplantation) indicated identical HLA haplotypes among affected relatives, with possible linkage of HN to the HLA-gene complex on 6p [Páramo et al., 1991; Izquierdo et al., 1992].

This study addresses familial HN and possible linkage to the HLA complex. Ultrasound studies of the kidneys were done on all available first-degree relatives of index cases to obtain an early diagnosis (relevant for clinical prognosis) and to establish genetic status. This was especially motivated because of non-specific and late occurrence of symptoms of hydronephrosis-related renal impairment, which (if noticed too late) requires nephrectomy rather than corrective surgical intervention, such as pyeloplasty.

METHODS

Four families with possible autosomal dominant inheritance are described. In all families clinical genetic examinations, ultrasound kidney examinations, and, in one family, prenatal diagnosis, were performed. HLA class I antigens were determined using NIH methods (microlymphocytotoxic tests). Finally, 15 HLA-A, 34 HLA-B, and 8 HLA-C antigens were typed. The other 18 antigens of the HLA class II (HLA-DR) were typed using PCR allelic-specific primers (DYNAL DR "low resolution" SSP kit [Miller et al., 1988; Olerup et al., 1992]). The details of the families are given in the following family reports.

Family I

The propositus II-2 (Fig. 1), born in 1969, was admitted at the age of 14 months because of high fever and severe illness due to acute pyelonephritis and septicemia. The IVP showed HN grade IV. Nephrectomy of the left kidney was indicated. During surgery, a dilated suppurative pelvicocalyceal system and multiple abscesses in the renal parenchyma were found. She was followed until adolescence. The right kidney appeared hypertrophic and descended by 2.5 vertebrae. The father, I-1, born in 1951, developed macroscopic hematuria at the age of 14 after a sudden fall on his back. The IVP showed HN grade IV, and nephrectomy of the left kidney was performed. There were no other cases of hereditary renal and/or ureteral malformations in this family. The proposita married at the age of 20. She had two first-trimester spontaneous abortions and during her third pregnancy we performed ultrasonographic examination of the fetal kidneys. In the 18th week, dilation of the pelvicocalyceal collecting system of the right kidney of the fetus was evident. This finding remained unchanged during the later pregnancy. A girl

*Correspondence to: A. Šantavá, M.D., Department of Medical Genetics and Fetal Medicine, Palacky University, I.P.Pavlova 6, 775 20 Olomouc, Czech Republic.

Received 8 February 1996; Accepted 9 August 1996

(III-I) weighing 3,400 g, 49 cm long, was born at term. Postnatal IVP confirmed HN grade IV. Pyeloplasty of the right kidney was performed four weeks after birth with an uneventful recovery.

The HLA typing is presented in the pedigree (Fig. 1). In this family, both father and daughter with unilateral congenital HN share a haplotype not shared by the prenatally diagnosed affected granddaughter (III-1).

Family 2

The propositus II-2, born in 1978, was operated on an acute ileus at the age of 2 years. At that time, a right HN in a solitary kidney was found and a resection pyeloplasty was performed. The renal parenchyma was greatly reduced and the region of the ureteropelvic junction was markedly constricted. Follow-up at age 14 showed a right kidney appearing elongated but with homogenous distribution of the radioisotope. The pedigree showed that the father (I-1) had pyeloplasty for left HN. An older brother (II-1) had a dilated pelvic system of the left kidney on ultrasound studies but this spontaneously resolved six months later. The younger sister (II-3) had normal renal ultrasound findings at age 12. HLA typing is given in Figure 2. An identical haplotype was found in the father and in both sons. The other paternal haplotype was inherited by the unaffected daughter.

Family 3

The propositus II-2, born in 1978, was admitted at the age of 12 years because of an enlarged submandibular lymph node. During clinical evaluation, renal ultrasonography showed advanced HN of the left kidney, necessitating nephrectomy; stenosis of the ureteropelvic junction was found. The right kidney showed grade III hydronephrosis requiring a resection pyeloplasty.

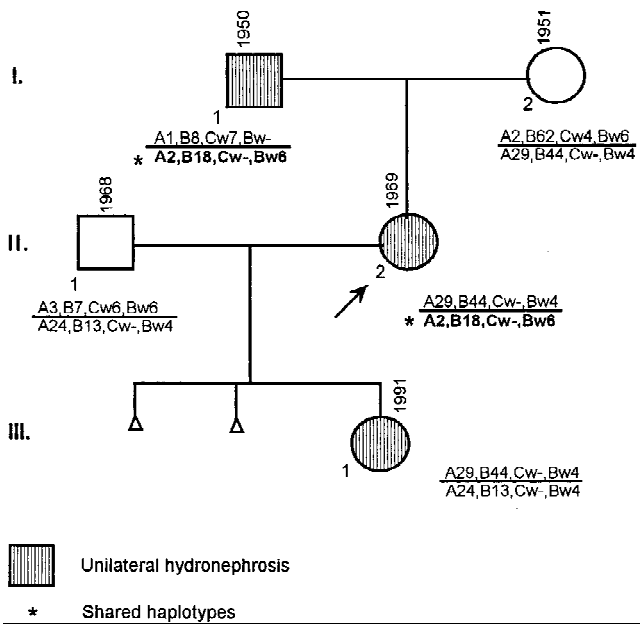

Fig. 1. Family 1—pedigree and HLA investigation.

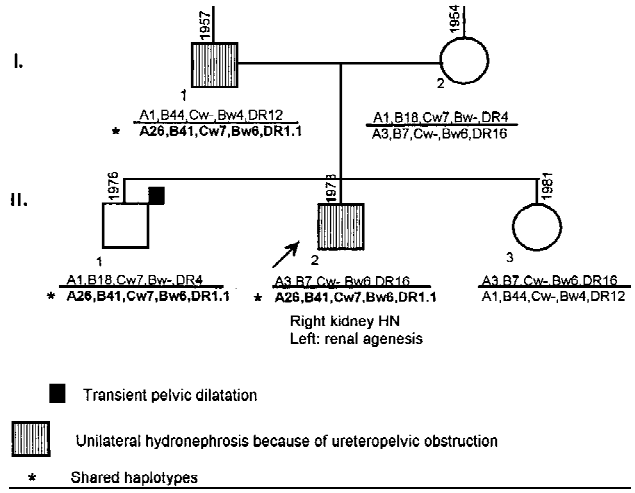

Fig. 2. Family 2—pedigree and HLA investigation.

The healthy sister (II-1) had a renal ultrasound study at age 12 which showed pelvic dilation on the right side and normal findings on the left. An IVP demonstrated grade II HN. This girl has been followed at six-month intervals for four years. The renal scintigraphy has remained normal and no intervention was needed. The mother (I-2), born in 1952, underwent an operation for left HN in her youth. The father died in an accident. HLA typing is in Figure 3. The two affected children (II-1 and II-2) show different haplotypes inherited from their affected mother (I-1).

Family 4

The propositus II-1, born in 1977, was healthy until the age of 12 years. He then developed left lumbar tenderness. An IVP showed a left-sided grade II-III HN. The renal parenchyma was reduced to 7 mm and the

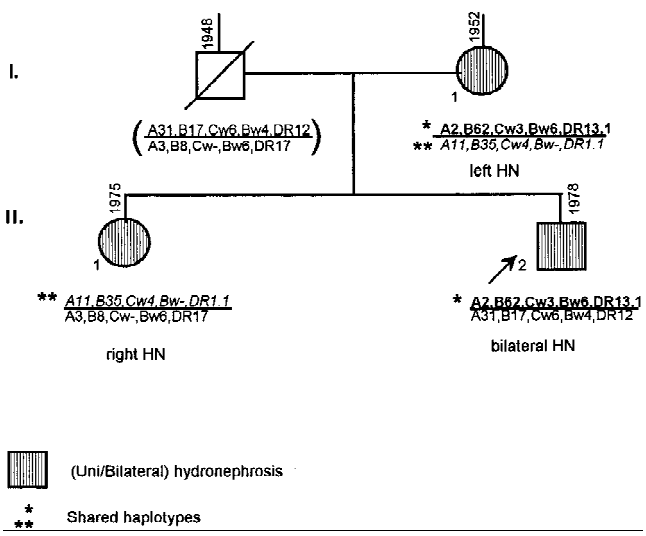

Fig. 3. Family 3—pedigree and HLA investigation.

calyces were markedly dilated. The right kidney was normal. A resection pyeloplasty was performed with satisfactory results. The sister (II-2) had normal renal findings at age 14. In his youth, the father (I-1), born in 1946, underwent a left nephrectomy for left-sided HN. The mother (II-2) showed normal renal ultrasound findings. HLA typing is given in Figure 4. The paternal haplotype shared with his similarly affected son differs from the haplotype he shares with his healthy daughter.

DISCUSSION

Familial occurrence of uni/bilateral hydronephrosis in sibs or with transmission from an affected parent to offspring has been reported [Aaron and Robbins, 1948; Jewell and Buchert, 1962; Grosse et al., 1973; Cohen et al., 1978; Dwoskin, 1979; Sengar et al., 1979; Buscemi et al., 1985] and reviewed by Páramo [1991]. If autosomal dominant inheritance with reduced penetrance is involved in this condition, there may be variability in age-of-onset and the importance of ultrasound renal studies in at least all first-degree relatives is clear. Early detection of HN offers the option of pyeloplasty before renal scarring leaves nephrectomy as the only option. The observation of haplo-identity for the HLA locus among affected members of multiplex families (affected members in one or more generations) indicated a possible linkage of the HN locus to the HLA locus on chromosome 6p [Izquierdo et al., 1992]. This was supported by the incidental findings of a (6,19)(p23.1q13.4) translocation in a fetus with bilateral multicystic renal dysplasia [Fryns et al., 1993]. The present results in two families with parent-to-offspring transmission of ureteropelvic junction obstruction and associated hydronephrosis indicate that there is not consistent HLA-haplotype identity between affected parents / affected offspring. Apparently, linkage to HLA-markers may not be suitable in all families for identifying relatives of patients with HN who have a risk of developing an identical disorder. However, in one small study two families do show HLA haplotype inheritance consistent with linkage.

The observation of "healthy" first-degree relatives with clinically significant degrees of ureteropelvic junction stenosis emphasizes the necessity for ultrasound studies to enable careful monitoring of incipient renal function loss and to allow timely pyeloplasty.

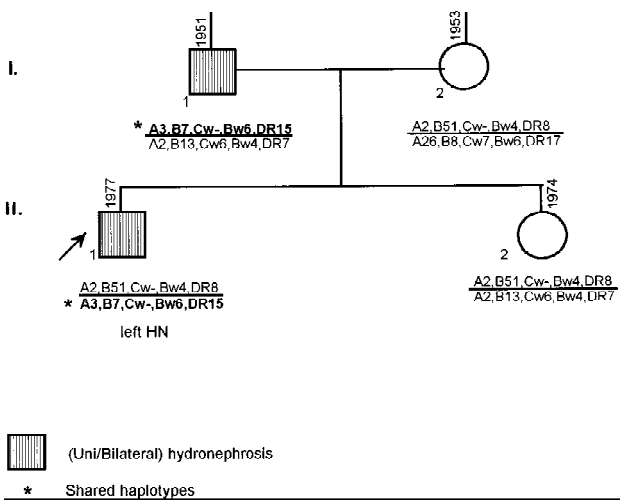

Fig. 4. Family 4—pedigree and HLA investigation.

REFERENCES

Aaron G, Robbins MA (1948): Hydronephrosis due to aberrant vessels: Remarkable familial incidence with report of cases. J Urol 60:702–705.

Buscemi M, Shanske A, Mallet E, Ozoktay S, Hanna MK (1985): Dominantly inherited ureteropelvic junction obstruction. Urology 26:568–570.

Cohen B, Goldman SM, Kopilnick M, Khurana AV, Salik JO (1978): Ureteropelvic junction obstruction: Its occurrence in 3 members of a single family. J Urol 10:361–364.

Dwoskin JY (1979): Ureteropelvic junction obstruction and sibling uropathology. Urology 13:153–158.

Fryns JP, Kleczkowska A, Moerman P, Vandenberghe K (1993): Hereditary hydronephrosis and the short arm of chromosome 6. Hum Genet 91:514–515.

Grosse FR, Kaveggia L, Opitz JM (1973): Familial hydronephrosis. Z Kinderheilk 114:313–322.

Izquierdo L, Porteous M, Páramo PG, Connor JM (1992): Evidence for genetic heterogeneity in hereditary hydronephrosis caused by pelviureteric junction obstruction, with one locus assigned to chromosome 6p. Hum Genet 89:557–560.

Jewell JH, Buchert WI (1962): Unilateral hereditary hydronephrosis: A report of four cases in three consecutive generations. J Urol 80:129–136.

Miller SA, Dykes DD, Polesky HF (1988): A simple salting out procedure for extracting DNA from human nucleated cells. Nucl Acids Res 16:215.

Olerup D, Zetterquist H (1992): HLA-DR typing by PCR amplification with sequence specific primers (PCR-SSP) in 2 hours: An alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens 39:225–235.

Páramo PG, Izquierdo L, Páramo P Jr, Llorente L, Diego A, Páez A, Gómez Ruíz JJ, Usón AC (1991): Genuine hereditary hydronephrosis in a three generation family. Eur Urol 20:293–300.

Sengar DPS, Rashid A, Wolfish NM (1979): Familial urinary tract anomalies. Association with the major histocompatibility complex in man. J Urol 121:194–197.